[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OF WAYNE STATE UNIVERSITY]

Epoxyethers. XV.[1,2] Ketals from Secondary Monohydric Alcohols

BY CALVIN L. STEVENS, ROBERT L. MCLEAN[3] AND ALFRED J. WEINHEIMER

RECEIVED NOVEMBER 20, 1957

The first two examples of ketals of secondary monohydric alcohols are reported. These ketals were prepared from the corresponding epoxyethers by acid-catalyzed opening of the epoxide ring with the secondary alcohols as shown by the conversion I → II. The fact that the α-hydroxyketal II, in the presence of acid catalyst, lost alcohol with the formation of the epoxyether I indicated an extraordinary amount of strain associated with this unique ketal. In contrast with the formation of the diisopropyl and the dicyclohexyl ketals, the di-*sec*-butyl ketal could not be prepared by this method. The *sec*-butyl epoxyether III gave only α-hydroxyketone IV when treated with *sec*-butyl alcohol in the presence of acid catalyst. The epoxyethers used in this investigation were conveniently prepared by a modification of the existing procedure and involved reaction of the α-haloketone with sodium alkoxide in liquid ammonia. This procedure was shown to be applicable with a variety of alcohols.

A ketal formed from a monohydric secondary alcohol previously has been unknown in the chemical literature.[4] The purpose of the present investigation was to determine whether the unusual driving force associated with the acid-catalyzed opening of an epoxyether with an alcohol could be used to prepare such a ketal. As a result a diisopropyl and a dicyclohexyl ketal were prepared.

Epoxyethers are known to react with alcohols with the formation of α-hydroxyketals. The ketals have been used to characterize epoxyethers since every epoxyether that has been isolated has reacted readily with an alcohol and the product formed invariably has been the result of attack of the alcohol upon the ketal carbon of the epoxyether. This reaction is acid catalyzed and in certain examples has been violently exothermic. The reaction may be considered as an acid-catalyzed alcohol interchange of a ketal the driving force of which is associated with the opening of the strained three-membered epoxide ring.

Acid-catalyzed reaction of the isopropyl epoxyether I with a large excess of isopropyl alcohol gave a 58% yield of the diisopropyl ketal II. The boiling point of the product indicated the material was not dimeric and the analyses indicated that one molecule of alcohol had added to the epoxyether. The infrared spectrum showed the presence of an alcohol (2.75 μ) and the absence of a carbonyl group. Further evidence for the structure was the easy hydrolysis of II to the parent hydroxyketone IV. The corresponding cyclohexyl epoxyether reacted with excess cyclohexanol in the presence of a catalytic amount of hydrochloric acid to give 45% of the dicyclohexyl ketal.

The diisopropyl ketal could be stored for long periods of time in scrupulously clean flasks. However, in flasks that had been cleaned previously with acid solution or by the deliberate addition of a small amount of aluminum chloride, the ketal II eliminated a molecule of isopropyl alcohol with the *formation of the epoxyether I*. The epoxyether could be recovered in 76% yield and the isopropyl alcohol was trapped and identified. This formation of epoxyether by intramolecular alcohol interchange is particularly interesting in view of the previous attempt to accomplish this transformation using the hydroxyketal[5] V. This hydroxyketal did lose a molecule of alcohol at high temperatures but the sole product was the vinyl ether VI. Another α-hydroxyketal VII has been shown to lose alcohol in still another manner[6] with the formation of VIII. These reactions indicate that formation of epoxyethers by intramolecular alcohol interchange of α-hydroxyketals is inherently very difficult. The fact that the interchange occurs readily with II must mean that this ketal has an extraordinary amount of strain and suggests that the preparation of ketals of secondary alcohols by ordinary methods will be difficult if not impossible.

An attempt to synthesize a di-*sec*-butyl ketal failed. The *sec*-butyl epoxyether III was dissolved in excess *sec*-butyl alcohol which contained a catalytic amount of acid. After one hour at the reflux temperature, the epoxyether was recovered unchanged (72%). After a similar solution had been heated to the reflux temperature for 24 hours, α-hydroxyisobutyrophenone could be isolated in 71% yield. One plausible mechanism for the formation of the α-hydroxyketone would involve the initial activation of the oxide ring by the acid catalyst followed by elimination of butylene and formation of the hydroxyketone as shown in formula IX instead of activation followed by attack of an external molecule of alcohol with formation of the ketal. This mechanism would compel the prediction that a non-proton acid like magnesium bromide would not give the usual rearrangement products[7] but rather would give the ketone and butylene. The prediction was not valid since magnesium bromide caused the epoxyether to rearrange as usual with the formation of the α-alkoxyketone X which was isolated in 46% yield. The infrared spectrum showed the carbonyl group (5.82 μ) of X not to be in conjugation with the benzene ring and the structure of X was proven by a second order Beckmann rearrangement of the oxime which gave acetophenone in 68% yield. The insoluble salts from the rearrangement mixture were acidified and from the organic portion was isolated 35% of the α-hydroxyisobutyrophenone (IV). The formation of IV in the rearrangement reaction

---

[1] Number XIV, *J. Org. Chem.* in press. A preliminary announcement of the ketals was made in *Chemistry & Industry*, 1321 (1957).

[2] Sponsored in part by the Office of Ordnance Research, U. S. Army.

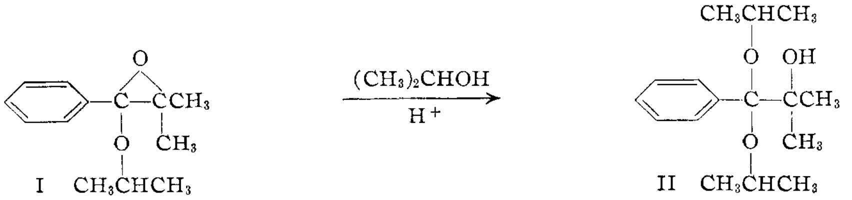
[3] Charles F. Kettering Foundation Fellow.

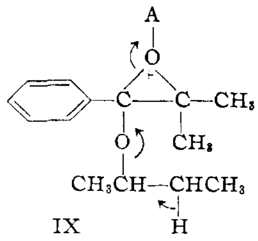
[4] A similar statement and a discussion of the problem has been made recently by C. A. MacKenzie and J. H. Stocker, *J. Org. Chem.*, **20**, 1695 (1955).

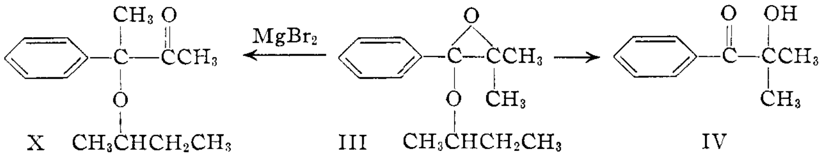
[5] C. L. Stevens and A. E. Sherr, *ibid.*, **17**, 1177 (1952).

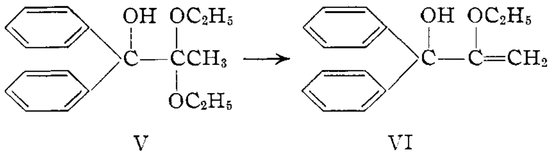
[6] C. L. Stevens, M. L. Weiner and R. C. Freeman, THIS JOURNAL, **75**, 3977 (1953).

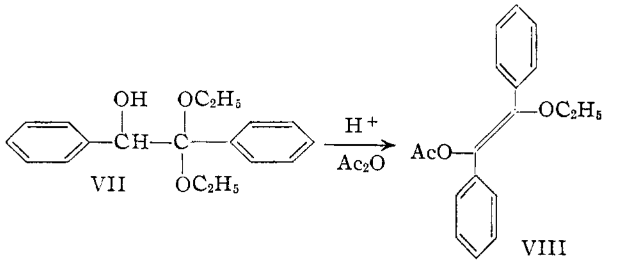
[7] C. L. Stevens and S. J. Dykstra, *ibid.*, **76**, 4402 (1954).











probably occurred by a mechanism similar to that represented in formula IX. The fact that no rearranged ketone X appeared along with IV in the alcoholysis reaction indicated that IV did not arise by the direct acid-catalyzed decomposition of the epoxyether but rather by slow dehydration of *sec*-butyl alcohol and subsequent reaction of the water with the epoxyether.

The isopropyl (I), cyclohexyl and *sec*-butyl (III) epoxyethers were prepared by a modification of the previously published procedure.[8] In the present work an ether solution of the bromoketone was added to a liquid ammonia solution which contained one equivalent of sodium alkoxide. The epoxyethers were formed in good yield and were stable in the liquid ammonia solution. The procedure was useful for the preparation of epoxyethers from *n*-butyl, allyl, benzyl and 2-methoxyethyl alcohols in addition to the three secondary alcohols. The properties of these epoxyethers are listed in Table I. The advantage of the liquid ammonia procedure lies in the ease with which the higher molecular weight sodium alkoxides can be prepared free of alcohol. Each of the epoxyethers gave the symmetrical α-hydroxyketal as listed in Table II.

Experimental

Preparation of the Epoxyethers. 1,2-Epoxy-1-alkoxy-2-methyl-1-phenylpropane.—Each of the epoxyethers listed in Table I was made according to the following directions. Sodium amide was prepared from 3.51 g. (0.15 g. atom) of metallic sodium, 250 ml. of liquid ammonia and a crystal of ferric nitrate to initiate the reaction. After disappearance of the blue color, 0.15 mole of alcohol dissolved in 150 ml. of dry ether was added slowly. Immediately following the additions of the alcohol 25 g. (0.11 mole) of α-bromoisobutyrophenone dissolved in 150 ml. of dry ether slowly was added. The mixture was stirred until all the liquid ammonia had escaped and the reaction had reached room temperature. The mixture was then refluxed for 30 minutes to remove residual ammonia and the ether was separated from the inorganic salts by centrifugation. After evaporation of the ether and flash distillation of the oily product to remove residual salts, the water-white material obtained was distilled at reduced pressure through a 20-cm. packed column.

Each of the epoxyethers reacted with 3,5-dinitrobenzoic acid to give 70–90% of the known derivative, α-hydroxyisobutyrophenone 3,5-dinitrobenzoate,[9] m.p. 150–152°.

α-Hydroxyisobutyrophenone Dialkylketals.—The epoxyethers that were made from primary alcohols were converted to the symmetrical ketal by acid-catalyzed (one drop of concentrated hydrochloric acid) reaction with an excess of the alcohol at the reflux temperature for one hour. The excess alcohol and the acid were removed under reduced pressure and the residual product purified by distillation through a 20-cm. packed column. The properties of the ketals are listed in Table II.

α-Hydroxyisobutyrophenone diisopropyl ketal was prepared from 16.6 g. (0.085 mole) of 1-isopropoxy-1,2-epoxy-2-methyl-1-phenylpropane (I), which was dissolved in 75 ml. of isopropyl alcohol and to this solution was added a drop of concentrated hydrochloric acid. The reaction was refluxed for three hours and then allowed to stand overnight. After removal of the excess isopropyl alcohol and hydrochloric acid under reduced pressure, the residual oil was distilled through a 20-cm. Vigreux column and gave 12.38 g. (57.6%) of pure material.

The dicyclohexyl ketal was prepared from 15 g. of epoxyether I, which was dissolved in 75 ml. of cyclohexanol and the reaction catalyzed with one drop of concentrated hydrochloric acid. The reaction was heated with stirring for one hour on a steam-bath, and then stirred overnight at room temperature. After the excess cyclohexanol was removed, the residual oil was distilled rapidly through a Claisen-type apparatus. In this way 5.72 g. (38.1%) of the starting material was collected, which was followed by an extremely high boiling fraction that amounted to 10.18 g. Redistillation gave 9.5 g. (45%) of pure dicyclohexyl ketal, b.p. 155–160° (0.2 mm.). This material was an extremely viscous, glass-like fluid which had the correct carbon and hydrogen content but failed to crystallize.

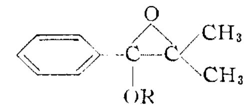
Treatment of α-Hydroxyisobutyrophenone Diisopropylketal with Aluminum Chloride.—A catalytic amount of aluminum chloride was added to 4.8 g. of α-hydroxyisobutyrophenone diisopropyl ketal and the mixture allowed to remain overnight at room temperature. Distillation gave 2.84 g. (76%), $n^{25}\text{D}$ 1.4764, b.p. 84–87° (5 mm.), of pure epoxyether. An infrared spectrum was identical with that of authentic material. Low boiling material, which was collected during the distillation, was treated with α-naphthyl isocyanate and gave the expected derivative of

---

[8] C. L. Stevens and E. Farkas, THIS JOURNAL, **74**, 618 (1952).

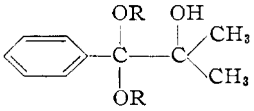
[9] C. L. Stevens and J. Tazuma, *ibid.*, **76**, 715 (1954).

TABLE I

EPOXYETHERS 

R	B.p. °C.	Mm.	$n^{25}D$	d^{25}	Yield, %	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I, Isopropyl	80–81	5	1.4779	0.9475	72	75.69	8.80	75.63	8.87
III, *sec*-Butyl	91–92	5	1.4785	0.9576	82	76.33	9.15	76.61	8.97
Cyclohexyl	88–90	0.5	1.5047	1.0108	58	78.01	9.00	78.31	9.00
n-Butyl	92–93	3	1.4802	0.9588	84	76.33	9.15	76.46	8.90
Allyl	90–91	5	1.4944	0.9880	78	76.44	7.90	76.50	8.05
2-Methoxyethyl	104–105	4	1.4875	1.0221	79	70.24	8.16	70.12	8.00
Benzyl	133–134	2	1.5398	1.051	63	80.28	7.13	80.21	7.36

TABLE II

α-HYDROXYKETALS 

R	M.p. or b.p. (mm.), °C.		$n^{25}D$	d^{25}_4	Yield, %	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Isopropyl	82–83	0.5	1.4889	0.9920	58	72.15	9.84	72.09	9.96
Cyclohexyl	155–160	.2			48	76.26	9.89	76.27	9.73
n-Butyl	93–94	.1	1.4821	.9665	90	73.43	10.27	73.41	10.52
Allyl	93–94	.5	1.5066	.9792	91	73.25	8.43	73.09	8.48
2-Methoxyethyl	54–55				64	64.41	8.78	64.34	8.60
Benzyl	82–83				66	79.53	7.23	79.59	7.12

isopropyl alcohol as shown by mixture melting point with an authentic sample and comparison of infrared spectra.

Reaction of 1-*sec*-Butoxy-1,2-epoxy-2-methyl-1-phenylpropane (III) with Excess *sec*-Butyl Alcohol.—To 12.29 g. (0.056 mole) of the epoxyether I was added 10 ml. of dry *sec*-butyl alcohol and one drop of concentrated sulfuric acid. The mixture was refluxed for one hour then cooled and 20 mg. of solid, anhydrous sodium carbonate added to neutralize the acid. The excess *sec*-butyl alcohol was then removed at reduced pressure and the residual oil distilled through a 12-cm. Vigreux column. Three fractions were collected. The first fraction consisted of 1.6 g., $n^{25}D$ 1.4800, of material boiling below 79° (2.2 mm.); the second fraction, 4.9 g., b.p. 79° (2.2 mm.), $n^{25}D$ 1.4805; and the third fraction 2.31 g., b.p. 79° (2.2 mm.), $n^{25}D$ 1.4810. The total recovery was 8.81 g. (72%) and from the infrared spectra and index of refraction it was apparent that quite pure starting material was recovered.

A similar experiment in which 15.09 g. (0.07 mole) of epoxyether, 15 ml. of *sec* butyl alcohol and one drop of concentrated sulfuric acid were refluxed for 24 hours gave the following results: Three fractions were collected upon distillation through a 12-cm. Vigreux column: the first fraction amounted to 2.27 g., b.p. 90–98° (4.8 mm.), $n^{25}D$ 1.4961; the second fraction, 7.56 g., b.p. 98–102° (4.8 mm.), $n^{25}D$ 1.5210; the third fraction, 0.43 g., b.p. 102–103° (4.8 mm.), $n^{25}D$ 1.5250. The physical constants and infrared spectra indicated that fraction one was a mixture of starting material and α-hydroxyisobutyrophenone while fractions two and three were α-hydroxyisobutyrophenone contaminated with starting material. There was no trace of a carbonyl band at 5.82 μ which would have indicated that some rearrangement had occurred.

The pot residue in each case consisted largely of the dimer of α-hydroxyisobutyrophenone, m.p. 185–186°, first reported by Favorskii.[10] It was found that as the period of reflux was extended the amount of this dimer obtained increased. In one experiment in which 8.61 g. (0.039 mole) of the epoxyether was refluxed in 30 ml. of *sec*-butyl alcohol containing two drops of concentrated sulfuric acid for 36 hours and then allowed to stand for an additional 24 hours before separation the yield of the dimer was 2.83 g., (46.8%).

For a comparison a pure sample of α-hydroxyisobutyrophenone IV was prepared by hydrolysis of an α-hydroxyketal. The yield from the pure crystalline dimethyl ketal[11] was 87%, b.p. 91–93° (1.9 mm.), $n^{25}D$ 1.5271–1.5279. The 3,5-dinitrobenzoate was prepared in 76% yield, m.p. 151–152°, identical with a previously prepared sample.[9] The semicarbazone[12] was prepared in 90% yield, m.p. 185–187°. The oxime was prepared in 45% and melted at 116–118°, which is ten degrees higher than previously reported.[12]

Anal. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31. Found: C, 67.08; H, 7.19.

A Beckmann rearrangement of the oxime according to the directions of Buck and Ide[13] gave acetone and 64% of benzonitrile, b.p. 55–57° (6 mm.), $n^{25}D$ 1.5255, which was hydrolyzed to benzoic acid.

α-Hydroxyisobutyrophenone acetate was prepared in 90% yield from the ketone, acetic anhydride and one drop of perchloric acid at 0°, m.p. 61–62°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.90; H, 6.84. Found: C, 69.81; H, 6.96.

Rearrangement of 1-*sec*-Butoxy-1,2-epoxy-2-methyl-1-phenylpropane (III).—Into 75 ml. of dry ether containing 1.11 g. (0.045 mole) of magnesium turnings was introduced 8.57 g. (0.045 mole) of ethylene bromide in portions to regulate the vigorous reaction. After the magnesium had reacted, 10 g. (0.045 mole) of the epoxyether in 75 ml. of ether was introduced. A gummy precipitate formed immediately and the mixture was stirred at the reflux temperature for 24 hours. Ten ml. of dioxane was added to precipitate the magnesium bromide and this mixture was refluxed an additional six hours then allowed to stand for 48 hours. The material was separated by centrifugation, after which the ether was evaporated and the residual oil distilled through a 10-cm. Vigreux column at reduced pressure. The distillation yielded 4.58 g. (45.8%), b.p. 93–96° (2 mm.), of material in three fractions of which the index of refraction at 25° varied from 1.4920 to 1.4933. Redistillation gave analytically pure 3-*sec*-butoxy-3-phenyl-2-butanone, b.p. 95–96° (2 mm.), $n^{25}D$ 1.4888.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.53. Found: C, 76.72; H, 9.15; O, 14.17.

---

[10] A. Favorskii, *J. Russ. Phys. Chem. Soc.*, **44**, 1339 (1912); *C. A.*, **7**, 986 (1913).

[11] C. L. Stevens and T. H. Coffield, THIS JOURNAL, **80**, 1919 (1958).

[12] E. Blaise and E. Herzog, *Compt. rend.*, **184**, 1332 (1927).

[13] J. S. Buck and W. S. Ide, THIS JOURNAL, **53**, 1912 (1931).

The salts, separated by centrifugation, when decomposed with water and acid produced 2.57 g. (34.5%), b.p. 85–90° (2 mm.), of α-hydroxyisobutyrophenone.

3-*sec*-Butoxy-3-phenyl-2-butanone was converted to the semicarbazone in 69% yield, m.p. 184–185°.

Anal. Calcd. for $C_{15}H_{23}N_3O_2$: C, 64.95; H, 8.36; N, 15.15; O, 11.54. Found: C, 65.08; H, 8.54; N, 15.12; O, 11.62.

The oxime was made from 0.2 g. (0.9 mm.) of ketone. The yield was 0.26 g. (72%) of crude material, m.p. 118–123°. Recrystallization from hexane gave an analytical sample, m.p. 123–125°.

Anal. Calcd. for $C_{20}H_{24}N_4O_5$: C, 59.99; H, 6.04; N, 13.99; O, 19.98. Found: C, 59.92; H, 5.96; N, 13.73; O, 19.68.

Beckmann Rearrangement of 3-*sec*-Butoxy-3-phenyl-2-butanone Oxime.—A mixture of 0.5 g. (2.3 millimoles) of 3-butoxy-3-phenylbutanone, 0.4 g. (5.75 mmoles) of hydroxylamine hydrochloride and 5 ml. of pyridine was allowed to stand overnight at room temperature then heated for two hours on the steam-bath. The pyridine was then removed *via* the vacuum pump and the residue treated with water. The oxime was subjected to the second-order Beckmann reaction according to the method of Buck and Ide.[13] The solid oxime from 0.5 g. of ketone was placed in 8 ml. of 10% sodium hydroxide solution and 0.69 ml. of benzenesulfonyl chloride added in two equal portions with shaking. The solid disappeared leaving an oil and when the odor of benzenesulfonyl chloride disappeared (approximately 30 minutes) the basic solution was extracted twice with 15-ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, filtered and evaporated to dryness. The residual oil was converted to the 2,4-dinitrophenylhydrazone derivative and 0.47 g. (68%), m.p. 240–244°, of product was obtained. The material was recrystallized from chloroform, m.p. 244–245°. A mixture melting point with authentic acetophenone 2,4-dinitrophenylhydrazone was not depressed.

Acknowledgment.—The authors wish to thank Dr. J. M. Vandenbelt and associates of Parke, Davis and Co. for the spectral data published here and C. E. Childs and associates of the same company for the analytical determinations.

DETROIT 2, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF PURDUE UNIVERSITY]

The Inductive Effects of Alkyl Groups as Determined by Desilylation Reactions

BY ROBERT A. BENKESER, RICHARD A. HICKNER AND DONALD I. HOKE

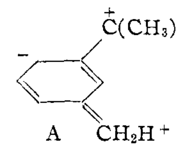
RECEIVED OCTOBER 7, 1957

It has been found that the rates of desilylation of trimethyl- and triethylphenylsilanes substituted in the *m*- position with alkyl groups increase in the order H < Me < Et < *i*-Pr < *t*-Bu. This is contrary to the decrease in rate for this series which is observed in the solvolysis of *m*-alkylphenyldimethylcarbinyl chlorides. It is rationalized that, at least in this instance, the desilylation reactions more closely approximate conditions realized in true aromatic substitutions. The carbinyl chloride series is apparently complicated in the present instance by unusual hyperconjugative or steric effects.

It is generally accepted that the inductive effect of alkyl groups increases moderately in the order Me < Et < *i*-Pr < *t*-Bu.[1] Likewise these same groups are thought to contribute hyperconjugative effects which tend to increase in the series *t*-Bu < *i*-Pr < Et < Me.[2a,b]

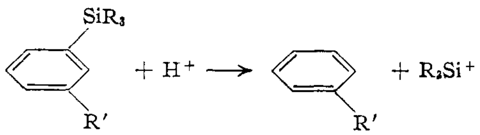
Recently Professor Brown and co-workers[3] have demonstrated that the electrical effects of alkyl groups can be studied conveniently by measuring the solvolysis rates of various alkyl substituted phenyldimethylcarbinyl chlorides in 90% aqueous acetone. Their results generally bear out the sequence shown above for the hyperconjugative series. Rather unexpectedly these authors noted, however, that the rates of solvolysis of the *m*-substituted alkylphenyldimethylcarbinyl chlorides *decrease* in the order Me > Et > *i*-Pr > *t*-Bu (Fig. 1.) This is just opposite to the gradual *increase* in rate one would predict for this series from a consideration of the inductive effects of the alkyl substituents. They[3] explain this anomaly in terms of a hyperconjugative effect in the *o*-position which is relayed to the reaction site by an inductive or field effect.

It should be noted that these results also can be explained in terms of a "normal inductive effect" counterbalanced by steric hindrance to solvation of the ring *ortho* to the alkyl substituents as suggested by Schubert and co-workers.[4]



A

Recently[5] it was demonstrated in this Laboratory that the removal of a trimethylsilyl group (desilylation) from an aromatic ring by acid is a reliable and convenient tool for studying electrical effects at a particular position in a benzene ring.



It was decided therefore, to study the rate of removal of the trimethylsilyl group from various *m*-substituted alkylphenyltrimethylsilanes to determine whether the same unexpected decreases in rate would be obtained as were found in the carbinyl chloride series. As an added check on the method, the rates of cleavage of the triethylsilyl series were also determined.

---

(1) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953.

(2) (a) E. D. Hughes, C. K. Ingold and N. Taher, *J. Chem. Soc.*, 949 (1940); (b) J. W. Baker, "Hyperconjugation," Oxford University Press, New York, N. Y., 1952.

(3) H. C. Brown, J. D. Brady, M. Grayson and W. H. Bonner, THIS JOURNAL, **79**, 1897 (1957).

(4) W. A. Sweeney and W. M. Schubert, *ibid.*, **76**, 4625 (1954); **79**, 910 (1957); see also *J. Org. Chem.*, **21**, 119 (1956).

(5) R. A. Benkeser and H. R. Krysiak, THIS JOURNAL, **76**, 6353 (1954); see also C. Eaborn, *J. Chem. Soc.*, 4858 (1956).